

Polyarthrititis:

Differential diagnosis:

- 1) rheumatoid arthritis
- 2) SLE
- 3) seronegative spondyloarthropathies
- 4) Henoch-Schonlein purpura
- 5) sarcoidosis
- 6) tuberculosis
- 7) pseudogout
- 8) viral infection: EBV, HIV, hepatitis, mumps, rubella

Jaccoud's arthropathy



The picture shows joint subluxations and swan neck deformities, caused by recurrent episodes of synovitis that **damage tendon sheaths** and **slings** resulting in joint deformity but, in this case, there is no bone deformity.

Jaccoud's arthropathy is seen in:

- 1) SLE
- 2) Rheumatic fever
- 3) Parkinson's disease, and
- 4) Hypocomplementaemic urticarial vasculitis.

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Systemic lupus erythematosus

Epidemiology:

- much more common in females (F:M = 9:1)
 - more common in Afro-Caribbean's* and Asian communities
 - onset is usually 20-40 years
 - incidence has risen substantially during the past 50 years (3 fold using ACR criteria)
- *It is said the incidence in black Africans is much lower than in black Americans -reason unclear

Pathophysiology:

- autoimmune disease, associated with **HLA B8, DR2, DR3**
- caused by immune system dysregulation leading to immune complex formation
- **immune complex** deposition can affect any organ including skin, joints, kidney & brain
- **HAO** hereditary angioneurotic oedema (deficiency of C1 esterase inhibitor): This leads to persistent activation of classical complement pathway and C4 levels are frequently low, If treatment fails to normalise C4 level, it is a high risk of developing SLE

Features: SLE is a multisystem, autoimmune disorder.

General features:

- 1) fatigue
- 2) fever
- 3) mouth ulcers
- 4) **lymphadenopathy**

Skin:

- 1) malar (butterfly) rash: **spares nasolabial folds**
- 2) Discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- 3) photosensitivity
- 4) Raynaud's phenomenon
- 5) livedo reticularis
- 6) non-scarring alopecia

Musculoskeletal:

- 1) arthralgia
- 2) non-erosive arthritis

Cardiovascular:

- 1) myocarditis
- 2) Libmansack endocarditis.

Respiratory:

- 1) pleurisy
- 2) fibrosing alveolitis

Renal:

- 1) proteinuria
- 2) glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

Neuropsychiatric:

- 1) anxiety, depression, psychosis ,seizures,
- 2) **subacute myelopathy** with **oligoclonal bands** in serum and CSF (paraplegia)

SLE investigations:

Immunology:

- 1) **99%** are **ANA** positive
- 2) **20%** are **RF** positive
- 3) **Anti-dsDNA**: highly specific (**> 99%**), but less sensitive (**70%**)
- 4) **Anti-Smith**: **most specific (> 99%)**, sensitivity (30%)
- 5) anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)

Monitoring:

- 1) **ESR**: during active disease.
The **CRP is characteristically normal** - a raised CRP may indicate underlying infection
- 2) complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement)
- 3) anti-dsDNA titers can be used for disease monitoring (but not present in all patients)

Discoid lupus erythematosus

- Benign disorder generally seen in younger females.
- It very rarely progresses to systemic lupus erythematosus (in less than 5% of cases).
- characterised by follicular keratin plugs and is thought to be autoimmune in aetiology

Features:

- 1) erythematous, raised rash, sometimes scaly
- 2) may be photosensitive
- 3) more common on face, neck, ears and scalp
- 4) lesions heal with atrophy, scarring (may cause scarring alopecia),pigmentation



Management:

- 1) topical steroid cream
- 2) oral antimalarials may be used second-line e.g. hydroxychloroquine,
- 3) avoid sun exposure

- SACLE is ANA positive in 60% patients.
- However, only 10-15% progress to SLE with moderate disease activity.
- 80% patients are anti-Ro antibody positive.
- Skin disease may occur as part of SLE, or be present as CLE (frequently without any systemic disease), and with variable chance of progression to SLE.
 - Discoid lupus erythematosus (DLE)
 - Subacute cutaneous lupus erythematosus (SACLE)
 - Acute cutaneous lupus erythematosus (ACLE)

are examples of CLE which may or may not progress to SLE. However, ACLE often accompanies flare of systemic disease & presents as diffuse erythema, maculopapular rash, photosensitivity & oral ulcers, while DLE presents as well defined scaly plaques heal with central scarring. انظر الجلدية مكتوبة احسن (p28)

Hydroxychloroquine ocular toxicity includes:

- Keratopathy
- Ciliary body involvement
- Lens opacities, and
- Retinopathy.

Retinopathy is the major concern; the others are more common but benign. The incidence of true hydroxychloroquine retinopathy is exceedingly low.

Risk factors include:

- Daily dosage of hydroxychloroquine
- Cumulative dosage
- Duration of treatment
- Coexisting renal or liver disease
- Patient age, and
- Concomitant retinal disease.

Patients usually complain of:

- 1) Difficulty in reading, decreased vision, missing central vision, glare, blurred vision,
 - 2) Light flashes, and metamorphopsia.
 - 3) They can also be asymptomatic.
 - 4) Most patients with advanced retinopathy have a bull's eye (also known as target, as in darts) fundoscopic appearance.
- All patients have field defects including paracentral, pericentral, and central and peripheral field loss.
 - **Regular screening** may be necessary to detect reversible premaculopathy.
 - **Cessation of the drug** is the only effective management of the toxicity.

Lupus nephritis

- Histologically, a number of different types of renal disease are recognised in SLE, with immune-complex mediated glomerular disease being the most common.
- The up to date International Society of Nephrology/Renal Pathology Society 2003 classification divides these into six different patterns:
 - ✗ I - minimal mesangial
 - ✗ II - mesangial proliferative
 - ✗ III - focal
 - ✗ IV - diffuse
 - ✗ V - membranous
 - ✗ VI - advanced sclerosis

I - minimal mesangial:

- Light microscopy ⇒ Glomeruli appear normal, but
- Immunofluorescence ⇒ demonstrates mesangial immune deposits.

II - Mesangial proliferative nephritis

- Presents clinically as microscopic haematuria and/or proteinuria.
- Hypertension is uncommon and nephrotic syndrome and renal impairment are very rarely seen.
- Biopsy demonstrates:
 - ⇒ Segmental areas of increased mesangial matrix and cellularity, with mesangial immune deposits.
 - ⇒ A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence.
- **The prognosis is good** and specific treatment is only indicated if the disease progresses.

III - Focal disease:

- More advanced, but still affects **< 50% of glomeruli**.
- Haematuria and proteinuria is almost always seen
- nephrotic syndrome, hypertension and elevated creatinine may be present.
- Biopsy demonstrates:
 - ⇒ Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving < 50% of glomeruli,
 - ⇒ typically with **focal subendothelial immune deposits**,
 - ⇒ with or without mesangial alterations
- It is further subdivided:
 - ✗ A: Active lesions: focal proliferative lupus nephritis
 - ✗ A/C: Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
 - ✗ C: Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
- **Prognosis** is variable.

IV - Diffuse glomerulonephritis:

- **The most common** and **severe** form of lupus nephritis.
- Haematuria and proteinuria are almost always present, and
- nephrotic syndrome, hypertension and renal impairment common.
- Biopsies demonstrate
 - ⇒ Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving more than 50% of all glomeruli,
 - ⇒ typically with **diffuse subendothelial immune deposits**,
 - ⇒ with or without mesangial alterations
- This class is divided into:
 - ⇒ **Diffuse segmental (IV-S)** when more than 50% of the involved glomeruli have segmental lesions, and
 - ⇒ **Diffuse global (IV-G)** when more than 50% of involved glomeruli have global lesions. (Segmental is defined as a glomerular lesions that involves less than half of the glomerular tuft)
- ✗ IV-S (A): Active lesions, diffuse segmental proliferative lupus nephritis
- ✗ IV-G (A): Active lesions, diffuse global proliferative
- ✗ IV-S (A/C): Active and chronic lesions, diffuse segmental proliferative and sclerosing lupus nephritis
- ✗ IV-S (C): Chronic inactive lesions with scars, diffuse segmental sclerosing lupus nephritis
- ✗ IV-G (C): Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
- **Immunosuppressive therapy** is required in these cases to prevent progressive to end-stage renal failure.

V - Membranous lupus nephritis:

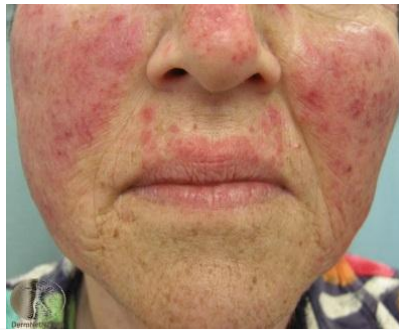
- Patients with membranous lupus nephritis tend to present with nephrotic syndrome.
- Microscopic haematuria and hypertension may also be seen.
- **Biopsies show**
 - ⇒ Global or segmental **subepithelial immune deposits** or their morphologic sequelae,
 - ⇒ with or without mesangial alterations
- It may occur in combination with class III or IV, in which case both are diagnosed.
- Progression is variable, and immunosuppression is not always needed.
- **In advanced sclerosis >90%** of glomeruli are globally sclerosed without residual activity.
- ✗ With regard to the management of lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function.
- ✗ This can provide a histological classification as well as information regarding activity, chronicity and prognosis.
- ✗ **Cyclophosphamide**, **mycophenolate mofetil** and **azathioprine** reduce mortality in proliferative forms of lupus glomerulonephritis.

Drug-induced lupus

- In drug-induced lupus not all the typical features of SLE are seen,
- with renal and nervous system involvement being unusual
- It usually resolves on stopping the drug.

Features:

- 1) Arthralgia, fever, serositis
- 2) Myalgia, skin (e.g. malar rash) , papular purpuric erythematous
- 3) and pulmonary involvement (e.g. pleurisy) are common
- 4) **ANA positive in 100%,**
- 5) **Anti- dsDNA negative**
- 6) **anti-histone** antibodies are found in **80-90%**
- 7) **anti-Ro, anti-Smith** positive in around **5%**



A woman with drug-induced lupus

Most common causes

- 1) procainamide
- 2) hydralazine

Less common causes

- 1) isoniazid, pyrazinamide
- 2) **minocycline, statin, anti TNF alpha, INFs, sulfasalazine**
- 3) phenytoin

SLE in pregnancy:

- risk of maternal autoantibodies crossing placenta leads to condition termed **neonatal lupus erythematosus**
- neonatal complications include **congenital heart block** (permanent & need PPM)
- strongly associated with **anti-Ro (SSA) antibodies**

Mixed connective tissue disease

- Features of;
 - ☒ **SLE,**
 - ☒ **systemic sclerosis** and
 - ☒ **polymyositis**
- **Anti-RNP** positive

Antiphospholipid syndrome

- **Acquired disorder characterised by:**
 - 1) a predisposition to both venous and arterial thromboses,
 - 2) recurrent fetal loss and
 - 3) thrombocytopenia
 - 4) False positive VDRL.
- A key point is that antiphospholipid syndrome causes a paradoxical rise in the APTT.
- This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features:

- 1) venous/arterial thrombosis
- 2) recurrent fetal loss
- 3) **thrombocytopenia, prolonged APTT** (not corrected with addition of normal plasma)
- 4) livedo reticularis
- 5) pre-eclampsia, pulmonary hypertension
- 6) It may occur as a primary disorder or secondary to other conditions, most commonly SLE

Associations other than SLE

- 1) other autoimmune disorders
- 2) lymphoproliferative disorders
- 3) phenothiazines (rare)

Management - based on BCSH guidelines

- 1) **initial venous thromboembolic events:** **warfarin** with a **target INR of 2-3 for 6 months**
- 2) **recurrent venous thromboembolic events:** **lifelong warfarin**;
If occurred whilst taking warfarin then increase **target INR to 3-4**
- 3) **arterial thrombosis** should be treated with **lifelong warfarin** with **target INR 2-3**

Diagnosis:

APAS is present if the patient has:

- Anticardiolipin antibodies or lupus anticoagulant on two occasions over a period of 12 weeks

And either has had

- A thrombus, or
- A history of recurrent **< 10 week pregnancy loss** or
- One pregnancy loss **> 10 weeks** in gestation
when other causes of pregnancy loss have been excluded

Patients with APAS and another autoimmune condition are said to have secondary APAS, while those with APAS where no associated autoimmune condition can be identified are said to have primary APAS.

In pregnancy the following complications may occur:

- 1) recurrent miscarriage
- 2) IUGR
- 3) pre-eclampsia
- 4) placental abruption
- 5) pre-term delivery
- 6) venous thromboembolism

Management:

- **low-dose aspirin** should be commenced **once the pregnancy is confirmed** on urine testing
- **LMWH:** ⇒ Started once a fetal heart is seen on ultrasound.
⇒ Discontinued at 34 weeks gestation

These interventions increase the live birth rate 7-fold

Extractable nuclear antigens:

- specific nuclear antigens, usually associated with being **ANA positive**

Examples:

- anti-Ro: Sjogren's syndrome, SLE, congenital heart block
- anti-La: Sjogren's syndrome
- anti-Jo 1: polymyositis
- anti-scl-70: diffuse cutaneous systemic sclerosis
- anti-centromere: limited cutaneous systemic sclerosis

Rheumatoid arthritis

- peak onset = 30-50 years, although occurs in all age groups
- F:M ratio = 3:1
- prevalence = 1%
- some ethnic differences e.g. high in Native Americans
- associated with HLA-DR4 (especially Felty's syndrome)

Rheumatoid arthritis diagnosis:

NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.

2010 American College of Rheumatology criteria:

Target population; Patients who

- 1) Have at least 1 joint with definite clinical synovitis
- 2) With the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis

(Add score of categories A-D; a **score of 6/10** is needed definite rheumatoid arthritis)

RF = rheumatoid factor

ACPA = anti-cyclic citrullinated peptide antibody

Factor	Scoring	
A. Joint involvement	1 large joint	0
	2 - 10 large joints	1
	1 - 3 small joints (with or without involvement of large joints)	2
	4 - 10 small joints (with or without involvement of large joints)	3
	10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	< 6 weeks	0
	> 6 weeks	1

X-ray changes in Rheumatoid arthritis:

Early x-ray findings

- soft-tissue swelling
- loss of joint space
- **juxta-articular osteopenia**

Late x-ray findings:

- **periarticular erosions**
- **subluxation**

Poor prognostic features:

- 1) rheumatoid factor positive
 - 2) anti-CCP antibodies
 - 3) HLA DR4
 - 4) poor functional status at presentation
 - 5) X-ray: early erosions (e.g. after < 2 years)
 - 6) extra articular features e.g. nodules
 - 7) insidious onset
- In terms of gender there seems to be a split in what the established sources state is associated with a poor prognosis. However both the American College of Rheumatology and the recent NICE guidelines (which looked at a huge number of prognosis studies) seem to conclude that **female gender is associated with a poor prognosis**.

Rheumatoid factor

- RF is a **circulating antibody** (usually **IgM**) which reacts with **the Fc portion of the patients own IgG**
- RF can be detected by either:
 - 1) **Rose-Waaler test**: sheep red cell agglutination
 - 2) **Latex agglutination test** (less specific)
- RF is positive in 70-80% of patients with rheumatoid arthritis,
- **high titre levels** are associated with **severe progressive disease**
- **but NOT a marker of disease activity**

Other conditions associated with a positive RF:

- 1) **Sjogren's syndrome** (around 100%)
- 2) **Felty's syndrome** (around 100%)
- 3) **Cryoglobulinemia II & III 40-100%**
- 4) Infective endocarditis (= 50%)
- 5) SLE (= 20-30%)
- 6) Systemic sclerosis (= 30%)
- 7) General population (= 5%)
- 8) rarely: TB, HBV, EBV, leprosy

Extra-articular complications with Rheumatoid arthritis:

A) **Respiratory:**

- 1) pulmonary fibrosis,
- 2) pulmonary nodules
- 3) Caplan's syndrome: massive fibrotic nodules with occupational coal dust exposure
- 4) pleurisy
- 5) pleural effusion,
- 6) bronchiectasis (especially non smokers) ,
- 7) bronchiolitis obliterans,
- 8) complications of drug therapy e.g. methotrexate pneumonitis, sulfasalazine, gold,
- 9) infection (possibly atypical) secondary to immunosuppression

B) **ocular:**

- 1) **keratoconjunctivitis sicca** (most common)
- 2) episcleritis (erythema)
- 3) scleritis (erythema and pain)
- 4) keratitis
- 5) corneal ulceration,
- 6) steroid-induced cataracts,
- 7) chloroquine retinopathy

C) osteoporosis

D) **IHD**: RA carries a similar risk to **type 2 DM**

E) increased risk of infections

F) depression

Less common complications:

1) Amyloidosis (AA)

2) **Felty's syndrome**

RA + splenomegaly + low white cell count+ leg ulcer in chronic seropositive RA

Management of Rheumatoid arthritis:

- The management of rheumatoid arthritis (RA) has been revolutionized by the introduction of disease-modifying therapies in the past decade.
- NICE has issued and released general guidelines in 2009.
 - ☒ Pts with joint inflammation should start a combination of DMARD **ASAP**.
 - ☒ Other important treatment options include analgesia, physiotherapy and surgery.

Initial therapy:

In the 2009 NICE guidelines it recommends that;

- ☒ patients with newly diagnosed active RA **start a combination of DMARDs (including methotrexate and at least one other DMARD)**, plus **short-term glucocorticoids**

1) DMARDs:

- 1) **Methotrexate** is the most widely used DMARD.
Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- 2) **sulfasalazine**
- 3) **leflunomide**
- 4) **hydroxychloroquine**

2) TNF-inhibitors: (can cause Drug induced lupus)

- the current indication for TNF-inhibitor is an inadequate response to at least 2 DMARDs including methotrexate,

A) **Etanercept:**

- ☒ recombinant human protein,
- ☒ acts as a decoy receptor for TNF- α ,
- ☒ SC,
- ☒ can cause demyelination,
- ☒ risks include reactivation of TB (less than Infliximab & Adalimumab, in first 3 months)

B) **Infliximab:**

- ☒ monoclonal antibody,
- ☒ binds to TNF- α and prevents it from binding with TNF receptors,
- ☒ IV,
- ☒ risks include reactivation of TB

C) **Adalimumab:**

- ☒ monoclonal antibody,
- ☒ SC

3) Rituximab:

- anti-CD20 monoclonal antibody,
- results in B-cell depletion
- two intravenous infusions(1g each) are given 2 weeks apart
- infusion reactions are common

4) Abatacept: a cytotoxic lymphocyte antigen 4 (CTLA 4) homologue

- **not currently recommend by NICE**
- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion

Methotrexate

An antimetabolite which inhibits DHFR **dihydrofolate reductase**, an enzyme essential for the synthesis of purines and pyrimidines

Indications:

- 1) rheumatoid arthritis
- 2) psoriasis
- 3) acute lymphoblastic leukaemia ALL

Adverse effects:

- 1) mucositis
- 2) myelosuppression
- 3) methotrexate pneumonitis (**first few months** of starting, should be **stopped & never** given)
- 4) pulmonary fibrosis
- 5) liver cirrhosis

Pregnancy:

- women should avoid pregnancy for at least 3 months after treatment has stopped
- BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

Prescribing methotrexate:

- Methotrexate is a drug with a high potential for patient harm.
 - It is therefore important that you are familiar with guidelines relating to its use;
- 1) methotrexate is taken weekly, rather than daily
 - 2) FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs **before starting treatment** and repeated **weekly** until therapy stabilised, thereafter patients should be monitored **every 2-3 months**'
 - 3) **Folic acid 5mg** once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose ???? some sources said folic acid 5 mg/day
 - 4) the **starting dose** of methotrexate is **7.5 mg weekly** (source: BNF)
 - 5) only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
 - 6) **avoid prescribing trimethoprim or cotrimoxazole** concurrently;
⇒ **Increases risk of marrow aplasia**

Azathioprine

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis.
- A thiopurine methyltransferase (**TPMT**) test may be needed to look for individuals prone to azathioprine toxicity (11% have low TPMT).

Adverse effects:

- 1) bone marrow depression
- 2) nausea/vomiting
- 3) pancreatitis
- 4) A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

Rheumatoid arthritis in pregnancy

- Rheumatoid arthritis (RA) typically develops in women of a reproductive age.
- Issues surrounding conception are therefore commonly encountered.
- There are no current published guidelines regarding how patients considering conception should be managed although expert reviews are largely in agreement.

Key points:

- 1) Patients with early or poorly controlled RA should be advised to defer conception until their disease is more stable
- 2) **RA symptoms** tend to **improve in pregnancy** but only **resolve in a small minority**.
- 3) Patients tend to have a flare following delivery
- 4) **Methotrexate** is **not safe in pregnancy** and needs to be stopped at least 3 months before conception
- 5) **Leflunomide** is **not safe in pregnancy**
- 6) **Sulfasalazine** and **hydroxychloroquine** are **considered safe in pregnancy**
- 7) Interestingly studies looking at pregnancy outcomes in patients treated with **TNF- α blockers** **do not show any significant increase in adverse outcomes**. It should be noted however that many of the patients included in the study stopped taking TNF- α blockers when they found out they were pregnant
- 8) **Low-dose corticosteroids** **may be used in pregnancy** to control symptoms
- 9) **NSAIDs** may be used **until 32 weeks** but after this time should be withdrawn due to the **risk of early close of the ductus arteriosus**
- 10) Patients should be referred to an obstetric anaesthetist due to the risk of **atlanto-axial subluxation**

Still's disease in adults:

- typically affects 16-35 year old
- typically RF negative

Features:

- 1) arthralgia, Fever
- 2) elevated serum ferritin
- 3) rash: **salmon-pink, maculopapular**
- 4) **lymphadenopathy**
- 5) rheumatoid factor (RF) and anti-nuclear antibody (ANA) **negative**

Felty's syndrome

- 1) (RA + splenomegaly + low white cell count+ leg ulcer) in longstanding RA
- 2) RF +ve 100%

Raynaud's

- Raynaud's phenomena may be:
 - ☒ Primary ⇒ Raynaud's disease or
 - ☒ secondary ⇒ Raynaud's phenomenon
- Raynaud's disease typically presents in young women (e.g. 30 years old) with symmetrical attacks

Factors suggesting underlying connective tissue disease:

- 1) onset after 40 years
- 2) unilateral symptoms
- 3) rashes
- 4) presence of autoantibodies
- 5) features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
- 6) digital ulcers, calcinosis
- 7) very rarely: chilblains تورم الأصابع

Secondary causes:

- 1) connective tissue disorders:
 - ⇒ scleroderma (most common),
 - ⇒ rheumatoid arthritis,
 - ⇒ SLE,
 - ⇒ Sjogren's syndrome,
 - ⇒ dermatomyositis
- 2) leukaemia
- 3) type I cryoglobulinaemia, cold agglutinins
- 4) use of vibrating tools
- 5) drugs: oral contraceptive pill, ergot
- 6) cervical rib

Management:

- 1) first-line: calcium channel blockers e.g. nifedipine
- 2) IV prostacyclin infusions: effects may last several weeks/months

Sjogren's syndrome

- Autoimmune disorder affecting **exocrine glands** resulting in **dry mucosal surfaces**.
- It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around **10 years after** the initial onset.
- Sjogren's syndrome is much more common in **females (ratio 9:1)**.
- There is a marked increased risk of **lymphoid malignancy (40-60 fold)**

Features:

- 1) dry eyes: keratoconjunctivitis sicca
- 2) dry mouth
- 3) vaginal dryness
- 4) arthralgia
- 5) Raynaud's, myalgia
- 6) **sensory** polyneuropathy
- 7) RTA (usually subclinical)

Investigation:

- 1) RF positive in nearly 100% of patients
- 2) ANA positive in 70%
- 3) anti-Ro (SSA) antibodies in 70% of patients with PSS
- 4) anti-La (SSB) antibodies in 30% of patients with PSS
- 5) **Schirmer's test**: filter paper near conjunctival sac to measure tear formation
- 6) histology: focal lymphocytic infiltration
- 7) hyper**gammaglobulinaemia**, low C4

Management:

- 1) artificial saliva & tears
- 2) **pilocarpine** may stimulate saliva production

Diffuse Infiltrative lymphocytic syndrome (DILS)

- can present like Sjogren's syndrome:
- Parotid gland enlargement and sicca symptoms,
- Extraglandular manifestations are common
- Mostly **negative autoantibodies** (Unlike Sjogren's)
- Peripheral **motor** neuropathy, cranial nerve palsies and Aseptic meningitis can also occur.
- **Lymphocytic interstitial pneumonitis** is the **most serious** complication of DILS.

Seronegative spondyloarthropathies

Common features:

- 1) HLA-B27
- 2) RF negative - hence 'seronegative'
- 3) peripheral arthritis, usually asymmetrical
- 4) sacroiliitis
- 5) enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- 6) extra-articular manifestations:
 - ⇒ uveitis,
 - ⇒ pulmonary fibrosis (upper zone),
 - ⇒ amyloidosis,
 - ⇒ aortic regurgitation

Spondyloarthropathies:

- 1) ankylosing spondylitis
- 2) psoriatic arthritis
- 3) Reiter's syndrome (including reactive arthritis)
- 4) enteropathic arthritis (associated with IBD, pauciarticular, asymmetric related to disease activity)

Ankylosing spondylitis

Features:

- 1) a HLA-B27 associated spondyloarthropathy
- 2) It typically presents in males (5:1) aged 20-30 years old.
- 3) typically a young man who presents with lower back pain and stiffness of insidious onset
- 4) stiffness is usually worse in the morning and improves with exercise
- 5) the patient may experience pain at night which improves on getting up

Clinical examination:

- 1) reduced lateral flexion
- 2) Reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- 3) reduced chest expansion

Other features - the 'A's:

- 1) Anterior uveitis
- 2) Apical fibrosis
- 3) AV node block
- 4) Aortic regurgitation
- 5) Achilles tendonitis
- 6) Amyloidosis
- 7) cauda equina syndrome
- 8) peripheral arthritis (25%, more common if female)

Ankylosing spondylitis investigation:

- 1) Inflammatory markers (**ESR, CRP**) are typically raised
Although normal levels do not exclude ankylosing spondylitis
- 2) **HLA-B27** is of little use in making the diagnosis as it is positive in:
 - 90% of patients with ankylosing spondylitis
 - 10% of normal patients
- 3) **Spirometry** may show a **restrictive defect** due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.
- 4) **Plain x-ray** of the sacroiliac joints is the **most useful** investigation in establishing the diagnosis.

Radiographs may be normal early in disease, later changes include:

1. **sacroilitis**: subchondral erosions, sclerosis, fusion of sacroiliac joints
2. **squaring of lumbar vertebrae**
3. **bamboo spine** (late & uncommon)
4. **syndesmophytes**: due to ossification of outer fibers of annulus fibrosus
5. chest x-ray: **apical fibrosis**



40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



Ankylosing spondylitis with well formed syndesmophytes



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Management:

The following is partly based on the 2010 EULAR guidelines :

- 1) encourage regular exercise such as swimming
- 2) physiotherapy
- 3) **NSAIDs** are **the first-line treatment**
- 4) the **DMARD** drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement
- 5) the 2010 EULAR guidelines suggest: '**Anti-TNF therapy** should be given to patients with persistently **high disease activity** despite conventional treatments'
- 6) research is ongoing to see whether anti-TNF therapies as **etanercept and adalimumab** should be used earlier in the course of the disease

Reactive arthritis

- One of the **HLA-B27** (75%) associated seronegative spondyloarthropathies.
- It encompasses Reiter's syndrome, a term which described a classic triad of **urethritis**, **conjunctivitis** and **arthritis** following a **dysenteric illness** during the Second World War.
- Later studies identified patients who developed symptoms following a sexually transmitted infection (**post-STI**, now referred to as sexually acquired reactive arthritis, SARA).
- Reactive arthritis is defined as **an arthritis that develops following an infection where the organism cannot be recovered from the joint.**

Features:

- 1) typically develops within 4 weeks of initial infection
- 2) symptoms generally last around 4-6 months
- 3) arthritis is typically an asymmetrical oligoarthritis of lower limbs
- 4) dactylitis
- 5) Around 25% of patients have recurrent episodes
- 6) 10% of patients develop chronic disease
- 7) symptoms of urethritis
- 8) eye:
 - ✓ Conjunctivitis (seen in 50%),
 - ✓ anterior uveitis
- 9) skin:
 - ✓ circinate balanitis (painless vesicles on the coronal margin of the prepuce),
 - ✓ keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles)



Figure 1: Typical circinate pattern of pustular eruption over the glans penis



Keratoderma blenorrhagica

Epidemiology:

- 1) post-STI form much more common in men (e.g. 10:1)
- 2) post-dysenteric form equal sex incidence

The table below shows the organisms that are most commonly associated with reactive arthritis:

Post-dysenteric form	Post-STI form
Shigella flexneri Salmonella typhimurium, Salmonella enteritidis Yersinia enterocolitica Campylobacter	Chlamydia trachomatis

Management:

- 1) symptomatic: analgesia, NSAIDs, intra-articular steroids
- 2) sulfasalazine and methotrexate are sometimes used for persistent disease
- 3) symptoms rarely last more than 12 months

Psoriatic Arthropathy

- Psoriatic arthropathy correlates poorly with cutaneous psoriasis
- often precedes the development of skin lesions
- Around 10% of patients with skin lesions develop an arthropathy
- males and females being equally affected

Types: 5 patterns

- 1) rheumatoid-like polyarthritis: (30-40%, most common type)
- 2) Asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- 3) sacroilitis
- 4) DIP distal joint disease with nail disease (10%)
- 5) arthritis mutilans rare (severe deformity fingers/hand, 'telescoping fingers')

Management:

- **treat as rheumatoid arthritis**
- but better prognosis



Notice the nail changes on this image as well



X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.



This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

Osteoarthritis

- The first carpometacarpal joint is a frequent site of osteoarthritis in postmenopausal women,
- Tenderness, stiffness, crepitus, swelling and pain on abduction of the thumb
- Squaring of the hand, caused by swelling, radial subluxation of the metacarpal and atrophy of the thenar muscles is a characteristic clinical sign.

X-ray changes:

- 1) decrease of joint space
- 2) subchondral sclerosis & cysts
- 3) osteophytes forming at joint margins

Management:

NICE published guidelines on the management of osteoarthritis (OA) in 2014

- 1) all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- 2) **Paracetamol** and **topical NSAIDs** are **first-line analgesics**.
 - ⇒ **Topical NSAIDs** are indicated only for **OA of the knee or hand**
- 3) Second-line treatment is:
 - ⇒ oral NSAIDs/COX-2 inhibitors (short term),
 - ⇒ opioids,
 - ⇒ capsaicin cream and
 - ⇒ intra-articular corticosteroids
 - ⇒ A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors.
 - ⇒ These drugs should be avoided if the patient takes aspirin
- 4) non-pharmacological treatment options include supports and braces, TENS and shock absorbing insoles or shoes
- 5) if conservative methods fail then refer for consideration of joint replacement (TENS Transcutaneous electrical nerve stimulation)

What is the role of glucosamine?

- 1) normal constituent of glycosaminoglycans in cartilage and synovial fluid
- 2) a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported **significant short-term symptomatic benefits** including **significantly reduced joint space narrowing** and **improved pain scores**
- 3) more recent studies have however been mixed
- 4) the 2008 NICE guidelines **suggest it is not recommended**
- 5) a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to **limited evidence of cost-effectiveness**

Systemic sclerosis

- A condition of unknown aetiology
- characterised by **hardened**, **sclerotic** skin and other connective tissues.
- It is 4 times more common in females
- Lung involvement is a frequent complication of systemic sclerosis, and can be split into two main syndromes:
 - 1) A pulmonary vascular disorder evolving over time into relatively **isolated pulmonary hypertension**
 - 2) **Interstitial lung disease**.
- **Raynaud's phenomenon** is seen in 90-95% of patients with systemic sclerosis. It is the most common sign of vascular involvement and is often one of the earliest clinical manifestations.

A) **Limited cutaneous systemic sclerosis:** (CREST syndrome)

- Raynaud's may be first sign
- scleroderma affects **face** and **distal limbs** predominately
- associated with **anti-centromere antibodies** (are the most specific test for limited cutaneous systemic sclerosis)
- a subtype of limited systemic sclerosis is **CREST syndrome**
- **CREST syndrome:** Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

B) **Diffuse cutaneous systemic sclerosis:**

- scleroderma affects **trunk** and **proximal limbs** predominately
- associated with **scl-70 antibodies**, **poor prognosis**
- **HTN**, **lung fibrosis** (decreased **TLCO** is early marker), **pulmonary HTN** (isolated or with lung fibrosis) & **renal involvement** seen
- **Scleroderma renal crisis** (SRC) in up to 10% cases: may present with rapid onset renal failure, malignant hypertension, retinopathy, MAHA with schistocytes. HTN should be treated with an ACEi and calcium channel blockers can be added.

C) **Scleroderma (without internal organ involvement):**

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear

Antibodies:

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis



Diffuse cutaneous systemic sclerosis may lead to scleroderma renal crisis (SRC) in up to 10% cases. SRC may present with rapid onset renal failure, malignant hypertension, micro-angiopathic haemolytic anaemia with schistocytes. Patients may develop symptoms of fluid overload.

Other risk factors for SRC include corticosteroid use (prednisolone more than 15 mg/day), recent onset scleroderma (less than three years), and involvement of other systems.

The underlying pathology of SRC is vasospasm, and treatment involves starting ACE inhibitors.

Scleroderma by itself does not associate with interstitial nephritis, glomerulonephritis, and acute tubular necrosis.

Dermatomyositis

- inflammatory disorder causing:
 - 1) **symmetrical, proximal muscle weakness** and
 - 2) **characteristic skin lesions**
- may be idiopathic or associated with connective tissue disorders or underlying **malignancy** (typically **lung cancer**, found in 20-25% - more if patient older)
- **polymyositis** is a variant of the disease where **skin manifestations are not prominent**

Skin features:

- 1) photosensitive
- 2) macular rash over back and shoulder
- 3) **heliotrope rash** in the periorbital region
- 4) **Gotttron's papules** - roughened red papules over extensor surfaces of fingers
- 5) nail fold capillary dilatation

Other features:

- 1) Raynaud's
- 2) proximal muscle weakness +/- tenderness
- 3) respiratory muscle weakness
- 4) interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- 5) dysphagia, dysphonia

Investigations:

- 1) elevated CK
- 2) EMG
- 3) muscle biopsy
- 4) **ANA positive** in **60%**
- 5) **anti-Mi-2 antibodies** are highly specific for dermatomyositis, but are only seen in around **25%** of patients
- 6) **anti-Jo-1 antibodies** are not commonly seen in dermatomyositis - they are more common in **polymyositis** where they are seen in a pattern of disease associated with lung involvement, Raynaud's and fever

Management: **prednisolone**



The classic purple (heliotrope) rash is seen on sun-exposed areas, especially the eyelids, nose, cheeks, forehead, knees, knuckles and around the nail beds. The rash may be pruritic.



Typical mechanic's hands found in a subtype of polymyositis called **antisynthetase syndrome** or **Jo-1 syndrome**. Raynaud's phenomenon, Myositis, Fibrosing alveolitis, and typical mechanic's hands (thickened, cracking, and peeling skin).

Inclusion body myositis (IBM)

- An inflammatory condition that affects the over 50s
- Men > women.
- Proximal muscles and **finger flexors** are predominantly involved
- The onset of muscle weakness is generally gradual (over months or years).
- **Creatine kinase (CK) may be normal.**
- Electromyogram (EMG) shows a similar pattern in polymyositis and IBM
- IBM **not associated** with malignancy.
- Biopsy in IBM shows **intranuclear** or **cytoplasmic tubofilaments** on electron microscopy.
- Polymyositis and dermatomyositis show a much better response to steroids than IBM.

Behcet's syndrome

- A complex multisystem disorder associated with presumed autoimmune mediated inflammation of the **arteries** and **veins**.
- The precise aetiology has yet to be elucidated however
- **exacerbations and remissions**
- The classic triad of symptoms are:
 - ✓ oral ulcers,
 - ✓ genital ulcers and
 - ✓ anterior uveitis



Epidemiology:

- more common in the **eastern Mediterranean** (e.g. **Turkey**)
 - More common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
 - tends to affect young adults (e.g. 20 - 40 years old)
 - Associated with HLA B5 and MICA6 allele.
 - HLA B5 is associated with **ocular disease**;
 - HLA B12 is associated with recurrent **oral ulcers**.
 - around **30% of patients have a positive FH**
- *more specifically HLA B51, a split antigen of HLA B5

Features:

- 1) classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- 2) **thrombophlebitis, DVT** (no risk of embolism)
- 3) arthritis, **fever**
- 4) **aseptic meningitis, headache**
- 5) **abdo pain**, diarrhoea, colitis
- 6) **erythema nodosum**

Diagnosis:

- 1) no definitive test
- 2) diagnosis based on clinical findings
- 3) **positive pathergy test** is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)

TTT:

- **Corticosteroids** in conjunction with **immunosuppressants** like azathioprine, cyclosporine, and cyclophosphamide may be used in those with venous or arterial involvement (as the cause of clot is inflammation of the vessel wall).
- **Colchicines**
- Anticoagulants, antiplatelet are not recommended (**risk of pulmonary aneurysm rupture**)

Chronic fatigue syndrome

- Diagnosed after **at least 4 months** of **disabling fatigue** affecting **mental and physical** function **more than 50% of the time** in the absence of other disease which may explain symptoms

Features:

- more common in females
- past psychiatric history **not a risk factor**
- **Fatigue** is the central feature,
- other recognised features include
 - 1) sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
 - 2) muscle and/or joint **pains**
 - 3) headaches
 - 4) **painful lymph nodes** without enlargement
 - 5) sore throat
 - 6) **cognitive dysfunction**, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
 - 7) physical or mental exertion makes symptoms worse
 - 8) general malaise or 'flu-like' symptoms
 - 9) dizziness
 - 10) nausea
 - 11) palpitations

Investigation:

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin*, coeliac screening and also urinalysis

*children and young people only

Management:

- 1) **cognitive behaviour therapy** - **very effective**, number needed to treat = 2
- 2) **graded exercise therapy** - a formal supervised program, **not** advice to go to the **gym**
- 3) '**pacing**' - organising activities to avoid tiring
- 4) low-dose **amitriptyline** may be useful for poor sleep
- 5) referral to a pain management clinic if pain is a predominant feature
- 6) Better prognosis in children

Fibromyalgia

- a syndrome characterised by **widespread pain throughout the body with tender points at specific anatomical sites.**
- The cause of fibromyalgia is unknown.

Epidemiology:

- women are 10 times more likely to be affected,
- typically presents between 30-50 years old

Features:

- 1) chronic pain: at multiple site, sometimes 'pain all over'
- 2) lethargy
- 3) sleep disturbance, headaches, dizziness are common

Diagnosis:

- 1) Diagnosis is clinical
- 2) Sometimes refers to **the American College of Rheumatology classification criteria** which list 9 pairs of tender points on the body.
- 3) If a patient is tender in **at least 11 of these 18 points** it makes the diagnosis more likely

Management:

- 1) The management is often difficult and needs to be tailored to the individual patient.
- 2) A psychosocial and multidisciplinary approach is helpful.
- 3) Unfortunately there is currently a paucity of evidence and guidelines to guide practice.
- 4) The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.
 - 1) **explanation**
 - 2) **aerobic exercise:** has **the strongest evidence base**
 - 3) **cognitive behavioural therapy**
 - 4) medication: **pregabalin, duloxetine, amitriptyline**

Polymyalgia rheumatic (PMR)

Pathophysiology:

- overlaps with temporal arteritis
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

Features: Polymyalgia rheumatica/temporal arteritis

- Predominantly polymyalgia symptoms,
For example, proximal muscle pain, stiffness (no weakness)
Or
- Arteritis symptoms, for example, headaches, scalp tenderness and jaw claudication.
 - 1) typically patient > 60 years old
 - 2) usually rapid onset (e.g. < 1 month)
 - 3) aching, morning stiffness in proximal limb muscles (not weakness)
 - 4) mild polyarthralgia, lethargy, depression,
 - 5) low-grade fever, anorexia, night sweats, Wt loss

Investigations:

- ☒ ESR > 40 mm/hr
- ☒ CK and EMG normal (عكس ال myositis and polymyositis)
- ☒ reduced CD8+ T cells

Treatment: prednisolone e.g. 15mg/od - dramatic response

- Corticosteroids remain the mainstay of treatment for polymyalgia rheumatica (PMR).
- The starting dose depends on patient's weight and severity of symptoms.
- The optimum duration of treatment is uncertain and is largely guided by response to therapy.
- Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy.
- Bisphosphonates should be added for long term steroid therapy.
- The usual starting dose is 15 mg prednisolone per day. Patients should expect relief of symptoms within 24-72 hours.
- The dose should be increased if symptoms are not well controlled within one week.
- The effective starting dose should be maintained for two to four weeks after the patient becomes asymptomatic.
- Generally, the daily dose can be lowered by 1.0-2.5 mg every two to four weeks to find the minimum dose needed to maintain symptom suppression.
- Once the patient is reduced to 10 mg per day, the daily dose can be tapered by 1 mg every four weeks.
- Tapering should be guided by clinical response.
- Normalisation of inflammatory markers (especially erythrocyte sedimentation rate [ESR]) are helpful but should not set the guidelines for decreasing or stopping the treatment.

- **An isolated increase of ESR without symptoms during the course of treatment is not a valid reason to increase corticosteroid dose; however, a temporary delay in dosage reduction may be necessary.**
- **Approximately 50-75% of patients can discontinue corticosteroid therapy after two years of treatment**
- **Relapses are more likely to occur during the initial 18 months of therapy and within one year of corticosteroid withdrawal.**
- **Patients should be closely monitored for recurrence of symptoms throughout the period of corticosteroid tapering and until 12 months after therapy stops.**
- **Methotrexate and azathioprine have been used in patients with corticosteroid intolerance or as corticosteroid-sparing agents.**
- **These are generally reserved for patients in whom it has been difficult to reduce the prednisolone after prolonged high dosages (for example, 10 mg or more per day for more than a year).**
- **These agents should be added to the prednisolone initially, but with a view to slowly reduce and withdraw prednisolone.**
- **As with steroid therapy, azathioprine or methotrexate can be discontinued if there has been sufficient response.**

Vasculitides

Marked constitutional (systemic) features: fever, malaise and weight loss تذكر..... هـام
ANCA should always be done in suspected systemic vasculitis.

Large vessel: TT

- Temporal arteritis
- Takayasu's arteritis

Medium vessel:

- polyarteritis nodosa
- Kawasaki disease

Small vessel:

- 1) ANCA-associated vasculitides (Wegener's*, Churg-Strauss*, microscopic polyangiitis)
- 2) Henoch-Schonlein purpura
- 3) cryoglobulinaemic vasculitis

*may also affect medium-sized vessels

Large Vessel Vasculitides

Temporal arteritis

- Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica.
- Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.
- Temporal arteritis, although commonly affecting the temporal artery, is a vasculitis affecting medium and large sized arteries throughout the body, hence its other term 'giant cell arteritis'.

Features:

- 1) typically patient > 60 years old
- 2) usually rapid onset (e.g. < 1 month)
- 3) **Headache** (found in 85%)
- 4) **Jaw claudication** (65%)
- 5) visual disturbances secondary to **anterior ischemic optic neuropathy**
- 6) **tender, palpable temporal artery**
- 7) features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- 8) lethargy, depression, low-grade fever, anorexia, night sweats

Investigations:

- 1) raised inflammatory markers:
 - ✓ **ESR > 50** mm/hr (note ESR < 30 in 10% of patients).
 - ✓ **CRP** may also be elevated
- 2) temporal artery **biopsy**: skip lesions may be present
- 3) CK and EMG **normal**

Treatment:

- 1) **high-dose prednisolone** - there should be a dramatic response, if not the diagnosis should be reconsidered
- 2) Urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an **ophthalmologist**.
- 3) **Visual damage is often irreversible**

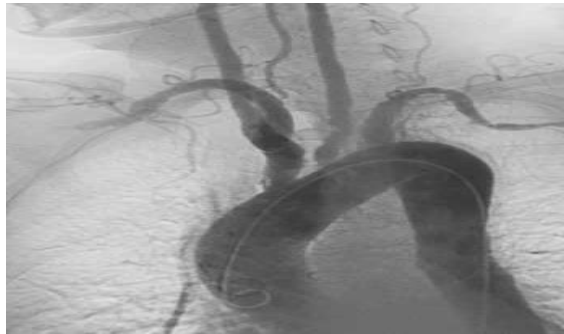
Large Vessel Vasculitides

Takayasu's arteritis

- Takayasu's arteritis is a large vessel vasculitis.
- It typically causes occlusion of the aorta and questions commonly refer to an absent limb pulse.
- It is more common in females and Asian people

Features:

- 1) systemic features of a vasculitis e.g. malaise, headache
- 2) unequal blood pressure in the upper limbs
- 3) Aortic regurgitation (around 20%)
- 4) carotid bruit
- 5) intermittent claudication



Angiography showing multiple stenoses in the branches of the aorta secondary to Takayasu's arteritis

Associations

- renal artery stenosis

Management:

- steroids

Medium Vessel Vasculitides

- Polyarteritis nodosa
- Kawasaki disease

Polyarteritis nodosa (PAN)

- A vasculitis affecting medium-sized arteries with necrotizing inflammation leading to **aneurysm formation**.
- PAN is more common in **middle-aged men** and is associated with **hepatitis B infection**

Features:

- 1) fever, malaise, arthralgia, weight loss
- 2) hypertension
- 3) **mononeuritis multiplex**, **sensorimotor polyneuropathy**
- 4) **testicular pain**
- 5) livedo reticularis
- 6) haematuria, renal failure
- 7) P-ANCA are found in around 20% of patients with 'classic' PAN
- 8) hepatitis B serology positive in 30% of patients



Livedo reticularis

Kawasaki disease

- This is a childhood febrile illness which results in inflammation of the **mucous membranes** with a **desquamative skin rash**.
- The condition is frequently self-limiting but it is important to recognise, as it causes **coronary arterial inflammation** resulting in **aneurysm formation** (25% of cases) which may present much later in life.
- Coronary disease can be prevented with treatment which includes **NSAIDs** and **gamma globulin infusion**.



The coronary angiogram reveals out-pouching (aneurysms) and would be typical of previous Kawasaki disease.

Small vessel

- 1) ANCA-associated vasculitides (Wegener's*, Churg-Strauss*, microscopic polyangiitis)
- 2) Henoch-Schonlein purpura
- 3) cryoglobulinaemic vasculitis

ANCA

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) - cytoplasmic (cANCA) and perinuclear (pANCA)

For the exam, remember:

- cANCA - Wegener's granulomatosis
- pANCA - Churg-Strauss syndrome + others (see below)

cANCA:

- most common target serine proteinase 3 (PR3)
- some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
- microscopic polyangiitis, positive in 40%

pANCA:

- most common target is myeloperoxidase (MPO)
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%

Other causes of positive ANCA (usually pANCA):

- inflammatory bowel disease (UC > Crohn's) &
- autoimmune hepatitis
- connective tissue disorders: RA, SLE, Sjogren's

Non-vasculitic causes of positive ANCA have **negative** anti-myeloperoxidase antibodies (MPO)

Granulomatosis with polyangiitis **(Wegener's granulomatosis)**

- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- an autoimmune condition associated with a **necrotizing granulomatous vasculitis**, affecting both the upper and lower **respiratory tract** as well as **the kidneys**

Features:

- 1) upper respiratory tract: epistaxis, sinusitis, nasal crusting
- 2) lower respiratory tract: dyspnoea, haemoptysis, cavitating lesions
- 3) rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
- 4) **saddle-shape nose** deformity
- 5) vasculitic rash, eye involvement (e.g. **proptosis**), cranial nerve lesions

Investigations:

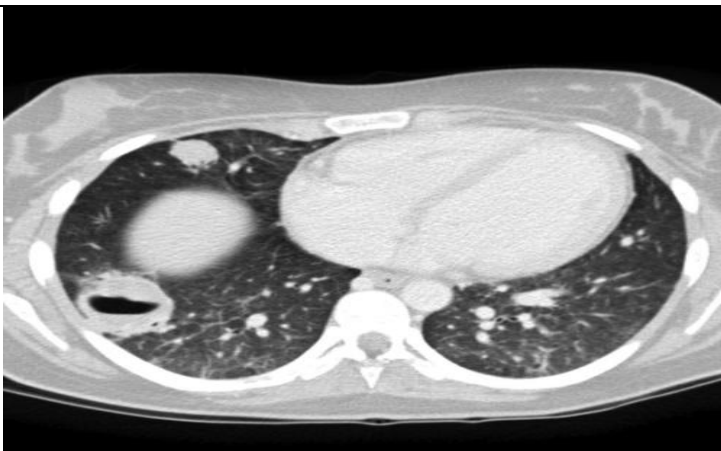
- 1) cANCA positive in > 90%, pANCA positive in 25%
- 2) chest x-ray: wide variety of presentations, including cavitating lesions
- 3) renal biopsy: **epithelial crescents** in Bowman's capsule

Management:

- 1) steroids
- 2) **cyclophosphamide** (90% response)
- 3) plasma exchange
- 4) median survival = 8-9 years



Chest x-ray from a young male patient with granulomatosis with polyangiitis. Whilst the changes are subtle it demonstrates a number of ill-defined nodules the largest of which projects over the dome of the right hemidiaphragm. This nodule appears to have a central lucency suggesting cavitation



CT of the same patient showing the changes in a much more obvious way, confirming the presence of at least 2 nodules, the larger of the two having a large central cavity and air-fluid level

Churg-Strauss syndrome

Churg-Strauss syndrome is an ANCA associated small-medium vessel vasculitis.

Features:

- 1) asthma
- 2) Blood eosinophilia (e.g. > 10%)
- 3) paranasal sinusitis
- 4) mononeuritis multiplex
- 5) pANCA positive in 60%
- 6) **Leukotriene receptor antagonists** may precipitate the disease

Cryoglobulinaemia

- Immunoglobulins which undergo reversible precipitation at 4 deg C dissolve when warmed to 37 deg C.
- One third of cases are idiopathic
- **Three types**
 - ☒ type I (25%): monoclonal
 - ☒ type II (25%): mixed monoclonal and polyclonal: usually with RF
 - ☒ type III (50%): polyclonal: usually with RF

Type I

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenström macroglobulinaemia

Type II

- mixed monoclonal and polyclonal: usually with RF
- associations: hepatitis C, RA, Sjogren's, lymphoma

Type III

- polyclonal: usually with RF
- associations: RA, Sjogren's

Symptoms (if present in high concentrations)

- 1) Raynaud's only seen in type I
- 2) cutaneous: vascular purpura, distal ulceration
- 3) arthralgia
- 4) renal involvement (**diffuse glomerulonephritis**)

Tests:

- **low complement** (esp. **C4**)
- **high ESR**

Treatment:

- 1) **immunosuppression**
- 2) **plasmapheresis**

Gout

- Gout is a form of microcrystal synovitis caused by the deposition of **monosodium urate monohydrate** in the synovium.
- Urate crystals are **needle-shaped**, and exhibit **strong negative birefringence** under polarised light microscopy
- It is caused by chronic hyperuricaemia (uric acid > 450 $\mu\text{mol/l}$)
- Acute Gout: 50% of all attacks and 70% of first attacks affect **first metatarsophalangeal joint**

Predisposing factors:

A) Decreased excretion of uric acid:

- 1) drugs*: diuretics
- 2) chronic kidney disease
- 3) lead toxicity

*aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels - the British Society for Rheumatology recommend it should be continued if required for cardiovascular prophylaxis

B) Increased production of uric acid:

- 1) myeloproliferative/lymphoproliferative disorder
- 2) cytotoxic drugs
- 3) severe psoriasis

C) Combined:

- Alcohol
- Exercise
- Glucose-6-phosphatase deficiency
- Aldolase B deficiency.

Gout: drug causes

- 1) thiazides, furosemide
- 2) alcohol
- 3) cytotoxic agents
- 4) pyrazinamide

Lesch-Nyhan syndrome:

- hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency
- x-linked recessive
- features: gout, renal failure, neurological deficits, learning difficulties, self-mutilation

Gout management:

A) Acute management:

- 1) NSAIDs
- 2) intra-articular steroid injection
- 3) Colchicine:
 - ⇒ has a slower onset of action
 - ⇒ The main side-effect is diarrhoea
 - ⇒ It inhibits microtubule polymerization by binding to tubulin, **interfering with mitosis.**
 - ⇒ Also inhibits neutrophil motility and activity
- 4) Oral steroids:
 - ⇒ May be considered if NSAIDs and colchicine are contraindicated.
 - ⇒ A dose of prednisolone 15mg/day is usually used
- 5) if the patient is already taking allopurinol it should be continued

B) Allopurinol prophylaxis:

- 1) allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- 2) initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of $< 300 \mu\text{mol/l}$
- 3) NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol

- 1) recurrent attacks:
 - ☒ the British Society for Rheumatology recommend In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year
- 2) tophi
- 3) renal disease
- 4) uric acid renal stones
- 5) prophylaxis if on cytotoxics or diuretics
- 6) patients with Lesch-Nyhan syndrome often take allopurinol for life

Allopurinol Hypersensitivity Syndrome (AHS)

- 0.1-0.4 % allopurinol treated patients develop allopurinol hypersensitivity syndrome (AHS)
- This can present as a severe multi-organ disease, with rash, hepatic and renal dysfunction, eosinophilia, and vasculitis, and has 20-25% mortality.
- Risk factors for this include renal impairment, thiazide diuretic use, and recent initiation of allopurinol (weeks/months).
- AHS is caused by the direct toxic effects of oxypurinol, or by T cell activating effects of oxypurinol, allopurinol. Patients with AHS should not be rechallenged with the drug.

- 2% of patients on allopurinol develop itchy maculopapular rashes
- 5-10% develop gastrointestinal dysfunction, and deranged liver function tests (LFTs)
- Allopurinol increases the anticoagulant effect of warfarin
- 20% of patients on allopurinol, who are prescribed amoxicillin or ampicillin, develop a rash.

Lifestyle modifications:

- 1) reduce alcohol intake and avoid during an acute attack
- 2) lose weight if obese
- 3) avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

Other points:

- 1) increased **vitamin C intake** (either supplements or through normal diet) may also decrease serum uric acid levels
- 2) **Losartan** has a specific **uricosuric** action and may be particularly suitable for the many patients who have coexistent hypertension
- 3) calcium channel blockers also increase uric acid levels, possibly by a renal vasodilatory effect



Well defined **punched-out juxta-articular erosions** related to both sides of the first metatarsal bone. This is a classical site for gout. **Rat Bite**

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase unlike allopurinol, which is a purine analogue inhibitor of xanthine oxidase.

Uricosuric agents like **probenecid** and **benzbromarone** work by blocking the anion exchanger URAT-1 at the apical brush border membrane of the proximal tubule in kidneys.

They also block urate reabsorption at the basolateral membrane of these cells by blocking GLUT 9 - the electrogenic glucose and fructose transport facilitator

Pseudogout

- Pseudogout is a form of microcrystal synovitis
- caused by the deposition of **calcium pyrophosphate dihydrate** in the synovium

Risk factors:

- 1) hyperparathyroidism
- 2) hypothyroidism
- 3) acromegaly
- 4) low magnesium, low phosphate
- 5) haemochromatosis, Wilson's disease

Features:

- 1) knee, wrist and shoulders most commonly affected
- 2) joint aspiration: **weakly-positively birefringent rhomboid shaped crystals**
- 3) x-ray: **chondrocalcinosis**

Management:

- 1) **aspiration** of joint fluid, to exclude septic arthritis
 - 2) NSAIDs or intra-articular, intra-muscular or oral steroids as for gout
- ☒ Calcium oxalate crystals - Bipyrnidal crystals that exhibit strong positive birefringence under polarised light
 - ☒ Calcium pyrophosphate crystals - Rhomboid crystals that exhibit weak positive birefringence under polarised light
 - ☒ Calcium hydroxyapatite crystals - Small, non-birefringent crystals visible only under electron microscopy.
-

Potential local side effects of corticosteroid injections include increased pain for the first couple of days, septic arthritis, subcutaneous atrophy (causing skin dimpling), skin depigmentation, accidental nerve injury and tendon rupture

Familial Mediterranean Fever

- Familial Mediterranean Fever (FMF, also known as recurrent polyserositis)
- An **autosomal recessive disorder**
- typically presents by the second decade
- It is more common in people of Turkish, Armenian and Arabic descent

Features:

- 1) attacks typically last 1-3 days
- 2) pyrexia
- 3) abdominal pain (due to peritonitis)
- 4) pleurisy
- 5) pericarditis
- 6) arthritis
- 7) erysipeloid rash on lower limbs

Management: **colchicine** may help

Osteomalacia

- normal bony tissue but **decreased mineral content**
 - ☒ **rickets** if when growing
 - ☒ **Osteomalacia** if after epiphysis fusion

Types:

- 1) vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- 2) vitamin D resistant; inherited
- 3) renal failure
- 4) liver disease, e.g. cirrhosis
- 5) drug induced e.g. anticonvulsants

Features:

- A) **rickets**: knock-knee, bow leg, features of hypocalcaemia
- B) **osteomalacia**: bone pain, fractures, muscle tenderness, proximal myopathy

Investigation:

- 1) low calcium, phosphate, 25(OH) vitamin D
- 2) raised alkaline phosphatase
- 3) x-ray:
 - ☒ Children - cupped, ragged metaphyseal surfaces;
 - ☒ Adults - translucent bands (Looser's zones or **pseudofractures**)

Treatment:

- calcium with vitamin D tablets

Vitamin D-resistant rickets:

- a **X-linked dominant** condition
- usually presents in infancy with failure to thrive,
- It is caused by impaired phosphate reabsorption in the renal tubules

Features:

- 1) failure to thrive
- 2) **normal calcium, low phosphate, elevated AL P**
- 3) x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis: is made by demonstrating **increased urinary phosphate**

Management:

- 1) high-dose **vitamin D** supplements
- 2) **oral phosphate** supplements

Osteopetrosis

- also known as **marble bone disease**
- rare disorder of **defective osteoclast** function resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common

Investigation:

Calcium, phosphate and ALP are **normal**

Management:

Stem cell transplant and
Interferon-gamma have been used for treatment

Osteoporosis

Risk Factors:

- Advancing age and female sex are significant risk factors for osteoporosis.
- Prevalence of osteoporosis increases from 2% at 50 years to
- more than 25% at 80 years in women

Assessing the risk of fragility fracture NICE guidelines 2012:

They advise that;

- ☒ all women aged ≥ 65 years and all men aged ≥ 75 years should be assessed
- ☒ Younger patients should be assessed in the presence of risk factors, such as:
 - 1) history of glucocorticoid use
 - 2) rheumatoid arthritis
 - 3) history of parental hip fracture
 - 4) history of falls, previous fragility fracture
 - 5) alcohol excess (> 14 units per week for women and > 21 units per week for men)
 - 6) current smoking
 - 7) low body mass index (< 18.5)
 - 8) other causes of secondary osteoporosis

Other risk factors:

- 1) sedentary lifestyle
- 2) premature menopause
- 3) Caucasians and Asians
- 4) endocrine disorders:
 - ☒ hyperthyroidism, hyperparathyroidism,
 - ☒ hypogonadism (e.g. Turner's, testosterone deficiency),
 - ☒ growth hormone deficiency,
 - ☒ diabetes mellitus
- 5) multiple myeloma, lymphoma
- 6) gastrointestinal disorders:
 - ☒ inflammatory bowel disease,
 - ☒ malabsorption (e.g. Coeliac's),
 - ☒ gastrectomy,
 - ☒ liver disease
- 7) chronic kidney disease
- 8) osteogenesis imperfecta
- 9) homocystinuria

Medications that may worsen osteoporosis (other than glucocorticoids):

- 1) long term heparin therapy
- 2) proton pump inhibitors
- 3) glitazones
- 4) aromatase inhibitors e.g. anastrozole (aromatase converts androgens into estrogens by aromatization, used in treatment of breast cancer & ovarian cancer in postmenopausal women and gynecomastia in men)

Methods of risk assessment

NICE recommend using a clinical prediction tool such as FRAX or QFracture to assess a patient 10 year risk of developing a fracture.

FRAX:

- estimates the 10-year risk of fragility fracture
- valid for patients aged 40-90 years
- based on international data so use not limited to UK patients
- assesses the following factors: age, sex, weight, height, previous fracture, parental fracture, current smoking, alcohol intake, glucocorticoids, rheumatoid arthritis, secondary osteoporosis,
- Bone mineral density BMD is optional, but clearly improves the accuracy of the results. NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result

QFracture:

- estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the QFracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 DM and TCAs

Interpreting the results of FRAX

☒ If the FRAX assessment was done without a BMD measurement the results (10-year risk of a fragility fracture) will be given and categorized automatically into one of the following:

- low risk: reassure and give lifestyle advice
- intermediate risk: offer BMD test
- high risk: offer bone protection treatment

☒ If the FRAX assessment was done with a BMD measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:

- 1) reassure
- 2) consider treatment
- 3) strongly recommend treatment

- If you use QFracture instead patients are not automatically categorized into low, intermediate or high risk.
- Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture.
- This data then needs to be interpreted alongside either local or national guidelines, taking into account certain factors such as the patient's age.

There are some situations where NICE recommend arranging BMD assessment (DEXA scan) rather than using one of the clinical prediction tools:

- 1) Before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).
- 2) in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or systemic glucocorticoids (>7.5 mg prednisolone or equivalent/day for ≥3 months)

When should we reassess a patient's risk?

NICE recommend that we recalculate a patient's risk (i.e. repeat the FRAX/QFracture):

- ☒ if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years
- , or
- ☒ when there has been a change in the person's risk factors

Investigations for secondary causes:

- If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted.
- NOGG recommend testing for the following reasons:
 - 1) exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
 - 2) identify the cause of osteoporosis and contributory factors;
 - 3) assess the risk of subsequent fractures;
 - 4) select the most appropriate form of treatment

The following investigations are recommended by NOGG:

- 1) History and physical examination
- 2) Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, phosphate, alkaline phosphatase , creatinine and liver transaminases
- 3) Thyroid function tests
- 4) Bone densitometry (DXA)

Other procedures, if indicated

- 1) Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- 2) Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 3) 25OHD
- 4) PTH
- 5) Serum testosterone, SHBG, FSH, LH (in men),
- 6) Serum prolactin
- 7) 24 hour urinary cortisol/dexamethasone suppression test
- 8) Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- 9) Isotope bone scan
- 10) Markers of bone turnover, when available
- 11) Urinary calcium excretion

So from the first list we should order the following bloods as a minimum for all patients:

- 1) full blood count
- 2) CRP
- 3) urea and electrolytes
- 4) liver function tests
- 5) bone profile
- 6) thyroid function tests

DEXA scan:

- T score: based on bone mass of young reference population
- T score of -1.0 means bone mass of one SD below that of young reference population
- Z score is adjusted for age, gender and ethnic factors

T score:

- ☒ > - 1.0 = normal
- ☒ - 1.0 to -2.5 = osteopaenia
- ☒ < -2.5 = osteoporosis

Management & assessing patient following fragility fracture:

The management of patients following a fragility fracture depends on age.

- ☒ Patients < 75 years of age:
 - ⇒ a DEXA scan should be arranged
 - ⇒ These results can then be entered into a FRAX assessment (along with the fact that they've had a fracture) to determine the patients ongoing fracture risk.
- ☒ Patients >75 years:
 - ⇒ a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'

Key points include:

- 1) Treatment is indicated:
 1. Following osteoporotic fragility fractures in postmenopausal women confirmed to have osteoporosis (T-score $\leq$ - 2.5 SD).
 2. 2014 NOGG guidelines suggest treatment is started in all women > 50 years who've had a fragility fracture', although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women
 3. In women $\geq$ 75 years, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- 2) vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- 3) **alendronate** is **first-line**
 - ⇒ Around 25% of patients cannot tolerate alendronate, usually due to upper GI problems.
 - ⇒ These patients should be offered risedronate or etidronate (see treatment criteria below)
- 4) strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

Treatment criteria for patients not taking alendronate:

- Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate
- These take into account a patients age, their T-score and the number of risk factors they have from the following list:
 - 1) parental history of hip fracture
 - 2) alcohol intake of 4 or more units per day
 - 3) rheumatoid arthritis

- **The most important thing to remember is:**

- 1) the T-score criteria for **risedronate** or **etidronate** are less than the others implying that these are **the second line drugs**
- 2) if alendronate, risedronate or etidronate cannot be taken then **strontium ranelate** or **raloxifene** may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score **< -3.5**)
- 3) the strictest criteria are for denosumab

A) **Vitamin D and calcium:**

- Poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures.
- may reduce rates in frail **ضعيف /سهل الكسر**, housebound patients

B) **Bisphosphonates:**

- 1) **alendronate, risedronate and etidronate** are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- 2) all three have been shown to **reduce the risk of both vertebral and non-vertebral fractures** although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- 3) **ibandronate** is a **once-monthly oral bisphosphonate**

C) **Raloxifene:**

- ✚ selective oestrogen receptor modulator (SERM)
- has been shown to prevent bone loss and to reduce the risk of **vertebral** fractures,
- but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of **thromboembolic events**
- may decrease risk of breast cancer

D) **Strontium ranelate:**

- **dual action** bone agent:
 - 1) increases deposition of new bone by **osteoblasts**
(Promotes differentiation of pre-osteoblast to osteoblast) and
 - 2) reduces the resorption of bone by **inhibiting osteoclasts**
- Concerns regarding the safety profile of strontium have been raised recently.
- It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it **should only be used by people for whom there are no other treatments for osteoporosis**

Adverse Effects:

- 1) **increased risk of cardiovascular events:**
⇒ Any history of CVD or significant risk of CVD is a contraindication
- 2) **increased risk of thromboembolic events:**
⇒ a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- 3) **may cause serious skin reactions** such as **Stevens Johnson syndrome**

E) **Denosumab:**

- human monoclonal antibody
- inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

F) Teriparatide:

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density
- but role in the management of osteoporosis yet to be clearly defined
- increased osteoblast activity, increased calcium absorption from the gut and reduced calcium excretion from the kidney

G) Hormone replacement therapy:

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

H) Hip protectors:

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

I) Falls risk assessment:

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients

Strontium ranelate: -----> Stevens Johnson syndrome----> TNE

تذكر الى كانوا بيعملوها

Penicillin, sulpha, phenytoin, cabamazepin, NSAID, allopurinol, Nevirapine

Glucocorticoid-induced Osteoporosis

- We know that one of the most important risk factors for osteoporosis is the use of corticosteroids.
- As these drugs are so widely used in clinical practice it is important we manage this risk appropriately.
- The most widely followed guidelines are based around the 2002 Royal College of Physicians (RCP) 'Glucocorticoid-induced osteoporosis: A concise guide to prevention and treatment'
- **The risk of osteoporosis is thought to rise significantly** once a patient is taking the equivalent of prednisolone 7.5mg a day for 3 or more months.
- It is important to note that **we should manage patients in an anticipatory**, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed.
- A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

Management of patients at risk of corticosteroid-induced osteoporosis:

The RCP guidelines essentially divide patients into two groups.

- 1) Patients > 65 years or those who've previously had a fragility fracture:
 - ⇒ should be offered **bone protection**
- 2) Patients < 65 years:
 - ⇒ should be offered a **DEXA scan** , with further management dependent:

T score	Management
> 0	Reassure
Between 0 and -1.5	Repeat DEXA scan in 1-3 years
Less than -1.5	Offer bone protection

The first-line treatment is **alendronate**. Patients should also be calcium and vitamin D replete.

Bisphosphonates

- Bisphosphonates are analogues of **pyrophosphate**,
- a molecule which decreases demineralisation in bone.
- They inhibit osteoclasts by reducing recruitment and promoting apoptosis.

Clinical uses:

- 1) prevention and treatment of osteoporosis (postmenopausal & steroid-induced)
- 2) hypercalcaemia
- 3) Paget's disease
- 4) pain from bone metastases

Adverse effects

- 1) oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
- 2) osteonecrosis of the jaw
- 3) increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate

The BNF suggests the following counselling for patients taking oral bisphosphonates:

- 'Tablets should be swallowed whole with plenty of water while sitting or standing;
- to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication);
- patient should stand or sit upright for at least 30 minutes after taking tablet'

Paget's disease of the bone

- Paget's disease is a disease of increased but uncontrolled bone turnover.
- It is thought to be **primarily a disorder of osteoclasts**, with **excessive osteoclastic** resorption followed by **increased osteoblastic** activity.
- Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

Predisposing factors:

- increasing age
- **male** sex
- northern latitude
- FH

Clinical features:

- only 5% of patients are symptomatic
- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- **raised (ALP)** - calcium and phosphate are typically **normal**
- **skull x-ray**: thickened vault, osteoporosis circumscripta
- **Angioid retinal streaks^{**}** in fundus

*usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Complications:

- 1) **deafness** (cranial nerve entrapment)
- 2) **bone sarcoma** (1% if affected for > 10 years)
- 3) **high-output cardiac failure** ,
- 4) Spinal cord compression
- 5) fractures,
- 6) skull thickening

Indications for treatment:

- 1) bone pain, fracture
- 2) skull or long bone deformity,
- 3) **periarticular Paget's**

Treatment:

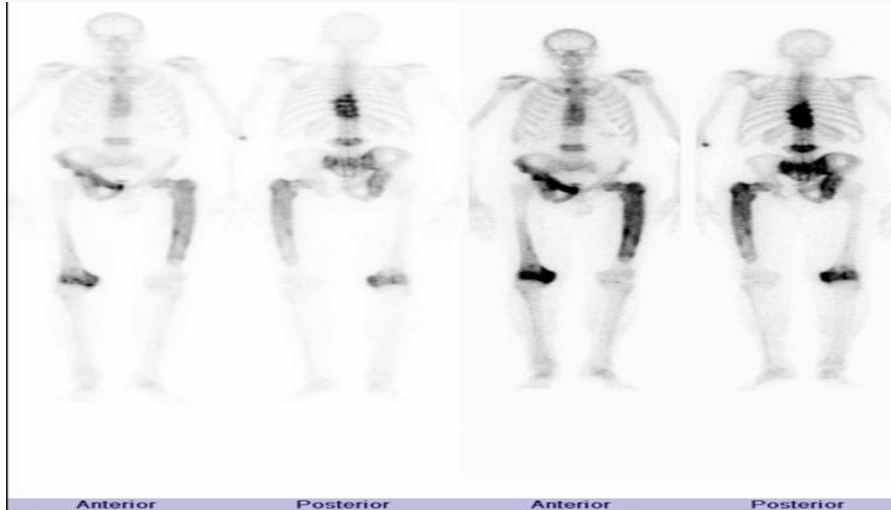
- 1) **bisphosphonate** (either oral risedronate or IV zoledronate)
- 2) calcitonin is less commonly used now



Image 1 The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

Image 2 Pelvic x-ray from an elderly man with Paget's disease

There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.



Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones



The bones are expanded with thickening of the cortex and coarsening of the trabecula pattern.



Paget's disease

Angioid streaks in retina

- Irregular dark red streaks radiating from the optic nerve head.
- They are caused by degeneration, calcification and breaks in Bruch's membrane.

Causes: SLAPPERS:

- 1) S - Sickle
- 2) L - Lead poisoning
- 3) A - Abetalipoproteinaemia/acromegaly
- 4) P - Pagets/phacomatoses (tuberous sclerosis, neurofibromatosis, Sturge-Weber)
- 5) P - Pseudoxanthoma elasticum
- 6) E - Ehlers-Danlos
- 7) R - Raised calcium or phosphate
- 8) S - Short people (dwarfism).

Septic arthritis

- most common organism overall is **Staphylococcus aureus**
- in young adults who are sexually active **Neisseria gonorrhoeae** should also be considered

Management:

- 1) **synovial fluid should be obtained** before starting treatment
- 2) Intravenous antibiotics which cover **Gram-positive cocci** are indicated.
- 3) The BNF currently recommends **flucloxacillin** or **clindamycin** if **penicillin allergic**
- 4) antibiotic treatment is normally be given for several weeks (BNF states **6-12 weeks**)
- 5) **needle aspiration** should be used to **decompress the joint**
- 6) **surgical drainage** may be needed if frequent needle aspiration is required

Elbow pain

Lateral epicondylitis (tennis elbow)	<u>Features:</u> 1) pain and tenderness localised to the lateral epicondyle 2) pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended 3) Episodes typically last between 6 months and 2 years. 4) Patients tend to have acute pain for 6-12 weeks
Medial epicondylitis (golfer's elbow)	<u>Features:</u> 1) pain and tenderness localised to the medial epicondyle 2) pain is aggravated by wrist flexion and pronation 3) symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement
Radial tunnel syndrome	Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse. <u>Features:</u> 1) symptoms are similar to lateral epicondylitis making it difficult to diagnose 2) however, the pain tends to be around 4-5 cm distal to the lateral epicondyle 3) symptoms may be worsened by extending the elbow and pronating the forearm
Cubital tunnel syndrome	Due to the compression of the ulnar nerve. <u>Features:</u> 1) initially intermittent tingling in the 4th and 5th finger 2) may be worse when the elbow is resting on a firm surface or flexed for extended periods 3) later numbness in the 4th and 5th finger with associated weakness
Olecranon bursitis	1) Swelling over the posterior aspect of the elbow. 2) There may be associated pain, warmth and erythema. 3) It typically affects middle-aged male patients.

Lateral epicondylitis:

- Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow').
- It is most common in people aged 45-55 years and typically affects the dominant arm.

Features:

- 1) pain and tenderness localised to the lateral epicondyle
- 2) pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- 3) episodes typically last between 6 months and 2 years
- 4) Patients tend to have acute pain for 6-12 weeks

Management options:

- 1) advice on avoiding muscle overload
- 2) simple analgesia
- 3) steroid injection
- 4) physiotherapy

Carpal tunnel syndrome:

Carpal tunnel syndrome is caused by compression of median nerve in the carpal tunnel.

History:

- pain/pins and needles in thumb, index, middle finger
- unusually the symptoms may 'ascend' proximally
- patient shakes his hand to obtain relief, classically at night

Examination:

- weakness of thumb abduction (abductor pollicis brevis)
- wasting of thenar eminence (NOT hypothenar)
- **Tinel's sign:** tapping causes paraesthesia
- **Phalen's sign:** flexion of wrist causes symptoms

Causes:

- idiopathic
- pregnancy
- oedema e.g. heart failure
- lunate fracture
- rheumatoid arthritis

Electrophysiology:

- motor + sensory: prolongation of the action potential

Treatment:

- corticosteroid injection
- wrist splints at night
- surgical decompression (**flexor retinaculum division**)

Dactylitis:

Dactylitis describes the inflammation of a digit (finger or toe).

Causes include:

- spondyloarthritis: e.g. Psoriatic and reactive arthritis
- sickle-cell disease
- other rare causes include tuberculosis, sarcoidosis and syphilis

De Quervain's tenosynovitis:

- a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed
- It typically affects females 30 - 50 years old

Features:

- pain on the radial side of wrist
- tenderness over the radial styloid process
- abduction of the thumb against resistance is painful
- **Finkelstein's test:** with the thumb is flexed across the palm of the hand, pain is reproduced by movement of the wrist into flexion and ulnar deviation

Management:

- analgesia
- steroid injection
- immobilisation with a thumb splint (**spica**) may be effective
- surgical treatment is sometimes required

Adhesive capsulitis **(Frozen shoulder)**

- a common cause of shoulder pain, It is most common in middle-aged females
- The aetiology is not fully understood.

Associations: ⇒ DM: up to 20% of diabetics may have an episode of frozen shoulder

Features:

- typically develop over days
- bilateral in up to 20% of patients
- external rotation is affected more than internal rotation or abduction
- both active and passive movement are affected
- patients typically have:
 - 1) a painful freezing phase,
 - 2) an adhesive phase and
 - 3) a recovery phase
- the episode typically lasts between 6 months and 2 years

Management:

- no single intervention has been shown to improve outcome in the long-term
- treatment options: ⇒ **NSAIDs, physiotherapy,**
⇒ Oral & intra-articular **corticosteroids**

Charcot neuroarthropathy

- In patients with **long-standing diabetes** and **peripheral neuropathy**, a red hot swollen foot should raise suspicion of Charcot neuroarthropathy.
- Charcot neuropathy presents as a warm, swollen, erythematous foot and ankle,
- important to exclude infection
- The majority of patients are in their 50-60s, and they often present in the latter stages of the disease.
- It can occur in association with a variety of conditions, including leprosy, poliomyelitis, rheumatoid arthritis, although today the most common cause is diabetes mellitus.
- The pathophysiology of Charcot neuroarthropathy is not completely understood, but is thought to start with peripheral neuropathy.
- The lack of pain sensation may mean that patients subject the foot joints (commonly the mid foot) to stress injuries that lead to the Charcot process.
- It is important to note however that about half of patients present with pain.

Four stages of Charcot neuropathy are recognised:

Stage 0 (inflammation)

⇒ characterised by erythema and oedema, but no structural changes.

Stage 1 (development)

- ⇒ bone resorption, fragmentation and joint dislocation
- ⇒ Swelling, warmth and erythema persist
- ⇒ But there are also radiographic changes such as:
- Debris formation at the articular margins,
 - osseous fragmentation and
 - joint disruption

Stage 2 (coalescence)

⇒ Bony consolidation, osteosclerosis and fusion are all seen on plain radiographs.

Stage 3 (reconstruction)

- ⇒ osteogenesis,
- ⇒ decreased osteosclerosis, progressive fusion
- ⇒ Healing and new bone formation occurs, and the deformity becomes permanent.

Investigations:

- Radiographs are an important part of investigating a patient with possible Charcot arthropathy.
- All radiographs should be taken in the weight-bearing position.
- MRI can demonstrate changes in the earlier stages of the condition, and is therefore important in allowing treatment to be instigated earlier.

Management:

In stages 0 and 1:

- ☒ The treatment is immediate immobilisation and avoidance of weight-bearing.
- ☒ A total contact cast is worn until the redness, swelling and heat subside (generally eight to 12 weeks, changed every one to two weeks to minimise skin damage).
- ☒ After this the patient should use a removable brace for a total of four to six months.

Diabetic cheiro-arthropathy

- A condition of limited joint mobility that occurs in diabetics.
- It is characterized by thickening of the skin resulting in contracture of the fingers.
- Cheiroarthropathy causes such limited motion of the fingers that the affected individual is unable to extend the fingers to flatten the hand fully.
- Typically both hands are affected by Cheiroarthropathy (**prayer sign**).
- Cheiroarthropathy has been reported in over 50% of patients with IDDM and approximately 75% of those with NIDDM.
- Cheiroarthropathy occurs more frequently in those with a longer history of diabetes.

Treatment:

- 1) Pain relief and/or anti-inflammatory drugs,
- 2) physiotherapy and
- 3) **tight** glycaemic control

Dupuytren's contracture is a condition of nodular hypertrophy and contractures of the superficial palmar fascia. Patients present with pitting, and nodule and thickening of the fascia of the hand.

Relapsing polychondritis (RP)



- The picture of his ear shows auricular chondritis, inflammation of the auricle with sparing of the earlobe. This is a characteristic finding of RP, because only the cartilaginous portion of the ear is affected, separating it from cellulitis/infection.
- Attacks are recurring and may last from a few days to several weeks.
- **Other manifestations include:**
 - 1) Nasal chondritis
 - 2) Ocular inflammation, and
 - 3) Arthritis.
- The sternoclavicular, costochondral and sternomanubrial joints are commonly involved.
- Costochondritis can manifest as pleuritic chest pain.
- Involvement of the tracheal cartilage may result in tracheal stenosis and result in life-threatening stridor.
- Renal disease is rare in RP

Hip pain in adults

Condition	Features
Osteoarthritis	1) Pain exacerbated by exercise and relieved by rest 2) Reduction in internal rotation is often the first sign 3) Age, obesity and previous joint problems are risk factors
Inflammatory arthritis	1) Pain in the morning, 2) Systemic features 3) Raised inflammatory markers
Referred lumbar spine pain	1) Femoral nerve compression may cause referred pain in the hip 2) Femoral nerve stretch test may be positive: ✓ Lie the patient prone ✓ Extend the hip joint with a straight leg then bend the knee ✓ This stretches the femoral nerve and will cause pain if it is trapped
Greater trochanteric pain syndrome (Trochanteric bursitis)	➤ Due to repeated movement of the fibroelastic iliotibial band ➤ Pain and tenderness over the lateral side of thigh ➤ Most common in women aged 50-70 years
Meralgia paraesthetica	➤ Caused by compression of lateral cutaneous nerve of thigh ➤ Typically burning sensation over antero-lateral aspect of thigh
Avascular necrosis	➤ Symptoms may be of gradual or sudden onset ➤ May follow high dose steroid therapy or previous hip fracture of dislocation
Pubic symphysis dysfunction	➤ Common in pregnancy ➤ Ligament laxity increases in response to hormonal changes of pregnancy ➤ Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. ➤ A waddling gait may be seen
Transient idiopathic osteoporosis	➤ uncommon condition sometimes seen in the 3rd trimester of pregnancy ➤ Groin pain associated with a limited range of movement in the hip ➤ Patients may be unable to weight bear ➤ ESR may be elevated

Ankle injury

Ottawa rules:

- The Ottawa Rules with for ankle x-rays have a sensitivity approaching 100%
- An ankle x-ray is required only if there is any pain in the malleolar zone and any one of the following findings:
 - 1) bony tenderness at the lateral malleolar zone (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
 - 2) bony tenderness at the medial malleolar zone (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
 - 3) inability to walk 4 weight bearing steps **immediately** after the injury and in the emergency department

There are also Ottawa rules available for both foot and knee injuries

Rotator cuff muscles:

SlitS - small t for teres minor

Supraspinatus

Infraspinatus

teres minor

Subscapularis

Muscle	Notes
Supraspinatus	aBDucts arm before deltoid Most commonly injured
Infraspinatus	Rotates arm laterally
teres minor	aDDucts & rotates arm laterally
Subscapularis	aDDuct & rotates arm medially

Marfan's syndrome

- Marfan's syndrome is an **autosomal dominant** connective tissue disorder.
- caused by a defect in the fibrillin-1 gene on chromosome 15 and affects around 1 in 3,000 people

Features:

- 1) tall stature with arm span to height ratio > 1.05
 - 2) high-arched palate
 - 3) arachnodactyly
 - 4) pectus excavatum
 - 5) pes planus
 - 6) scoliosis of > 20 degrees
 - 7) dural ectasia (ballooning of the dural sac at the lumbosacral level)
 - 8) Heart:
 - ✗ dilation of the aortic sinuses (seen in 90%) which may lead to:
 - 1) Aortic aneurysm,
 - 2) aortic dissection,
 - 3) aortic regurgitation,
 - ✗ Mitral valve prolapse (75%),
 - 9) lungs: repeated pneumothoraces
 - 10) eyes: upwards lens dislocation (superotemporal ectopia lentis), blue sclera, myopia
- The life expectancy of patients used to be around 40-50 years.
 - With the advent of regular **echocardiography monitoring** and **beta-blocker/ACE-inhibitor therapy** this has improved significantly over recent years.
 - Aortic dissection and other cardiovascular problems remain the leading cause of death however.

Homocystinuria

- a rare autosomal recessive disease
- Caused by deficiency of cystathionine beta synthase.
- This results in an accumulation of **homocysteine** which is then oxidized to **homocystine**.

Features:

- often patients have fine, fair hair
- musculoskeletal: may be similar to Marfan's - arachnodactyly etc
- neurological patients may have **learning difficulties**, **seizures**
- ocular: downwards (**inferonasal**) dislocation of lens
- increased risk of **arterial** and **venous thromboembolism**
- also **malar flush**, **livedo reticularis**

Diagnosis:

- Is made by the cyanide-nitroprusside test,
- which is also positive in cystinuria

Treatment:

Vitamin B6 (pyridoxine) supplements

Cystinuria

- Cystinuria is an autosomal recessive disorder
- Characterised by the formation of **recurrent renal stones**.
- It is due to a defect in the membrane transport of cystine, ornithine, lysine, arginine (mnemonic = COLA)

Genetics:

- chromosome 2: SLC3A1 gene,
- chromosome 19: SLC7A9

Features:

- recurrent renal stones
- are classically yellow and crystalline, appearing semi-opaque on x-ray

Diagnosis:

- cyanide-nitroprusside test

Management:

- 1) hydration
- 2) urinary alkalization
- 3) D-penicillamine

A 33-year-old teacher presents with a three week history of dry cough, low grade fever, and erythematous nodular lesions on the cheek, nose, forehead and chin.

Systemic examination is normal.

A chest x ray showed bilateral hilar adenopathy. The lesions on her face were biopsied and showed multiple non-caseating granulomata.

What is the most likely diagnosis?

- 1) **Lymphoma**
- 2) **Sarcoidosis**
- 3) **SIE**
- 4) **TB**
- 5) **Wegner**

Answer 2

This patient has got lupus pernio, a skin manifestation that is specific to sarcoidosis.

Differential diagnosis of bilateral hilar adenopathy:

- Sarcoidosis
- Lymphoma
- Tuberculosis
- Pneumoconiosis
- Berylliosis, and
- Fungal diseases like histoplasmosis.

Unlike in sarcoidosis, the granulomata in tuberculosis show caseating necrosis.

Differential diagnosis of lupus pernio:

- Wegener's granulomatosis
- Lymphoma cutis, and
- Cutaneous lupus.

The clinical presentation helps differentiate some lesions, but a biopsy may be required.

Wegener's granulomatosis patients usually present with symptoms of sinusitis, otitis, or nasal ulceration. The skin lesions include ulcers, nodules, and granuloma formation.

The lesions of lymphoma cutis can occur anywhere on the skin and typically appear as a pink-red to red-purple papule or plaque.

There are many cutaneous manifestations of systemic lupus erythematosus, but the two most common are discoid lesions and the butterfly rash:

- Discoid lupus lesions are circular with slightly raised, scaly hyper-pigmented erythematous rims and depigmented atrophic centres**
- The butterfly rash, with its characteristic location over the cheeks and nose, is typically photosensitive and appears as a slightly raised erythematous lesion.**

Frequently, these patients have accompanying arthralgias that suggest the diagnosis.